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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,894	04/25/2001	Patricia A. Billing-Medel	6083.US.D2	6734

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/841,894	BILLING-MEDEL ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-16,23-35,38 and 39* is/are pending in the application.

4a) Of the above claim(s) *23-32 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-16,33,35,38 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

1. This application now properly complies with the requirements for priority and priority is granted.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 10-16, 33, 35, 38 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of nucleic acids which are different from those disclosed in the specification. The genus includes variants for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named SEQ ID Nos 1-16. Thus, applicant has express possession of only these 16 nucleic acids in a genus which comprises hundreds of millions of different possibilities. Here, no common element or attributes of the sequences are disclosed, not even the presence of certain domains. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations is provided. Further, these claims encompass alternately spliced versions of the proteins, allelic variants including insertions and mutations, inactive precursor proteins which have a removable amino terminal end, and only specific amino acid sequences have been provided. No written description of alleles, of upstream or downstream regions containing additional sequence, or of alternative splice variants has been provided in the specification.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection

> because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the SEQ ID Nos 1-16 to comprise the sequence, to claim any 50% identical sequence or to any sequence which hybridizes to the sequence is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the 16 specific sequences, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely but its functional utility, as a PS108 polynucleotide, without any definition of the particular changes due to the % identity, or selectively hybridizing language claimed.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise SEQ ID Nos 1-16. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

3. The rejection under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 10-16, 30, 33 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by de Louvencourt et al (U.S. Patent 4,806,472)

In order to clarify the following rejection, the claim interpretation will be explicated. Claim 16 reads on a cell which is transfected with a recombinant expression system which must have a vector linked to a PS108 sequence ORF or fragment thereof. There is no minimum size limitation on the fragment of claim 10, so a fragment of only three nucleotides can potentially constitute an ORF, since many triplets can encode an amino acid.

De Louvencourt teaches an expression vector which has an EcoR1 site (see figure 2) which vector is in a host cell (see 4, lines 1-50). The EcoR1 site comprises

GAA. GAA is a fragment found in SEQ ID NO: 2, among other fragments which fragment encodes the amino acid, Glutamic acid. This fragment meets the claim requirements as discussed above.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 10-14 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Southern (U.S. Patent 6,054,270).

Southern teaches an array which comprises every possible 8 mer oligonucleotide placed in separate, isolated locations, which oligonucleotides are purified (column 5). These oligonucleotides are initially single stranded (column 12, example 7) and Southern teaches hybridization of 8-mers to the array to yield double stranded

molecules (column 12, example 7). These arrays would inherently and necessarily comprise every 8 mer fragment of SEQ ID Nos: 1-16.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to make the array of Southern since Southern expressly states "Applications include analyses of known point mutations, genomic fingerprinting, linkage analysis, characterization of mRNAs, mRNA populations and sequence determinations (abstract)". An ordinary practitioner, confronted with these many desirable uses of n-mer microarrays, would have been motivated to synthesize every 8-mer in order to perform these methodologies on cosmid or plasmids as taught by Southern (column 5)..

Response to Arguments

9. Applicant's arguments filed February 10, 2003 have been fully considered but they are not persuasive.

Applicant argues that the 102 rejection is improper because there is a lower limit on the size of the fragments, six nucleotides, and cites to page 13 of the specification. As Applicant correctly quotes, the specification states that "A "fragment" of a specified polynucleotide refers to a polynucleotide sequence which comprises a contiguous sequence of approximately at least about 6 nucleotides (see page 13 of specification)". The phrase "approximately at least about 6" is not definite, since it does not set a clear lower bound. The phrase "at least" typically indicates a minimum point. The phrase "at least" however, is contraverted by the term "about" which implies that values above and below 6 nucleotides are permitted. Further, the extent of variance

permitted by "about" is unclear in this context. Since nucleotides are whole numbers, "about 6" cannot be clearly defined because nucleotides cannot be split in half. Therefore, it is also unclear if "about 6" simply includes 5 or if it also includes 1-4 as well. In Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1218 (CAFC 1991), the CAFC stated, "The district court held claims 4 and 6 of the patent invalid because their specific activity limitation of "at least about 160,000" was indefinite". After review, the CAFC states "We therefore affirm the district court's determination on this issue." Thus, the CAFC found the phrase "at least about" indefinite where the metes and bounds of the term were not defined in the specification. Since de Louvencourt clearly teaches 3, which may be "at least about 6", this rejection stands.

Further de Louvencourt also teaches, in figure 3, the presence of a PstI site. This site has a sequence of CTGCAG. These six nucleotides are found in nucleotides approximately 95-100 of SEQ ID NO: 1. CTGCAG would encode Leucine-Glutamine. Thus, de Louvencourt inherently also teaches six nucleotides as expressly required by the specification in the vector.

Applicant then argues the 103 rejection over Southern by arguing that Southern does not teach the claimed sequences. Southern expressly suggests an array with EVERY POSSIBLE 8-mer. Of necessity, this set of 65,536 different oligomers necessarily encompasses every 8-mer in Applicant's sequence, since it represents the complete set of 8-mers. Therefore, this rejection is maintained.

Applicant argues that the 50% identical language complies with the written description requirement because this determination can be made using prior art

references, such as the programs in the Wisconsin group. Applicant argues that this readily available method to determine the nucleic acids encompassed by the claims places the inventors in possession of the claimed invention.

This argument is not found persuasive for two reasons. First, while it is superficially appealing to argue that the percent identity provides structure to the claims, in fact, methods of calculating percent identity vary based upon the algorithm chosen. This algorithm based variation renders the exact set of species encompassed by the genus less certain and the possession less defined. Further, even if a particular algorithm is selected, the genus size for a 258 base pair fragment such as SEQ ID NO: 1 would be immense. The calculation for a single point mutation within this sequence would result in 3 possible substitutions times 258 possible positions. For two changes, the calculation would be (3 x 258) (for the first position) multiplied by (3 x 257) for the second position. Thus, the calculation would be 3^{129} x 258 factorial divided by 129 factorial for 50% possible differences. This is 3.5×10^{61}. Since the number of atoms calculated to be in the universe ranges from 10^{78} to 10^{81}, the number of possible different sequences contained in the genus is very large indeed.

Second, when this immense genus is analyzed in the framework applied by the Federal Circuit in Lilly, Fiers, and Enzo, it is clear that there is no common feature which relates all members of the genus of sequences 50% identical to the specific SEQ ID NO. For example, SEQ ID NO: 6 has 178 nucleotides. These are CTTGGCCAAA ACTCAGCGT AGAAAACTTC CAGCACATTG GGGTGGAGGG CCTGCCTCAC TGGGTCCCAG TCCCCGCTC CTGTTAGCCC CATGGGGCTG CCGGGCTGGC

CGCCAGTTTC TGTTGCTGCC AAAGTYATGT GGCTCTCTGC TGCCACCCTG TGCTGCTGAG GTGCGTANTG CACAGCTGGG GGCTG.

Two members of the claimed genus are

CTTGGCCAAA ACTCAGCGT AGAAAACTTC CAGCACATTG GGGTGGAGGG CCTGCCTCAC TGGGTCCCAG TCCCCGCTC CTGTTAGC and

CC CATGGGGCTG CCGGGCTGGC CGCCAGTTTC TGTTGCTGCC AAAGTYATGT GGCTCTCTGC TGCCACCCTG TGCTGCTGAG GTGCGTANTG CACAGCTGGG GGCTG

Representing the first 88 and the second 88 nucleotides of this sequence. These two sequences are both 50% identical to SEQ ID NO: 6, but share no sequence identity with one another and have no common feature relating them to the genus. Further, without any functional recitation, there is are no necessary common elements which provide informative description of the members of the genus. In Lilly, an insulin sequence with about 80% homology to the prior art and which was functionally limited was found to lack descriptive support. Here, where a lower homology is used and no functional limitations are recited, there is a clear absence of possession of the entire claimed genus.

Lastly, the Written Description guidelines, in example 14, address the issue of percent identity. In that context, two requirements were necessary to comply with the written description requirement. The first was an expectation that the genus would not substantially vary. In the guidelines, this expectation was met with a 95% identity requirement. Here, with a 50% identity limitation, this expectation is not met. Second,

there is a functional requirement of catalytic activity which limits the scope of the genus. In the current claim there are no functional requirements for these nucleic acid sequences and therefore this limitation is not present in the current claim set.

For these reasons, the written description rejection is maintained.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

March 21, 2003